# A small-molecule TNIK inhibitor targets fibrosis in preclinical and clinical models

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## Abstract

Idiopathic pulmonary fibrosis (IPF) is an aggressive interstitial lung disease with a high mortality rate. Putative drug targets in IPF have failed to translate into effective therapies at the clinical level. We identify TRAF2- and NCK-interacting kinase (TNIK) as an anti-fibrotic target using a predictive artificial intelligence (AI) approach. Using AI-driven methodology, we generated INS018_055, a small-molecule TNIK inhibitor, which exhibits desirable drug-like properties and anti-fibrotic activity across different organs in vivo through oral, inhaled or topical administration. INS018_055 possesses anti-inflammatory effects in addition to its anti-fibrotic profile, validated in multiple in vivo studies. Its safety and tolerability as well as pharmacokinetics were validated in a randomized, double-blinded, placebo-controlled phase I clinical trial (NCT05154240) involving 78 healthy participants. A separate phase I trial in China, CTR20221542, also demonstrated comparable safety and pharmacokinetic profiles. This work was completed in roughly 18 months from target discovery to preclinical candidate nomination and demonstrates the capabilities of our generative AI-driven drug-discovery pipeline. An AI-generated small-molecule inhibitor treats fibrosis in vivo and in phase I clinical trials.